REMARKS

Applicants submit this response to the Office Action dated December 22, 2006. Claims 1-30, 43, and 44 have been withdrawn from consideration. Claim 31 has been amended to correct erroneous chemical consistent language, and no new matter is added. Applicants acknowledge that the rejection under 35 U.S.C. § 102 (b) as being anticipated by Danilenko et al., SU 539878, 1976, has been withdrawn.

The rejection of claims 31-42 under 35 U.S.C. § 112, first paragraph, was maintained because the specification, while being enabling for some inhibiting data, allegedly does not reasonably provide enablement.

In response to the applicants' arguments of November 27, 2006, the Examiner stated that there is no guidance regarding which diseases are mediated by the chemokine. The Examiner also provided several examples of inflammation of various tissues and the current treatment of such inflammation. In response, applicants request that the Examiner consider the current state of research and medical knowledge on the role of specific chemokine receptors in inflammation. The references are provided as exhibits and in the accompanying IDS form.

1. As reported by Reutershan, J., et al. in Drug News Perspect. 19:615-23 (2006), CXC chemokine receptor 2 (CXCR2) has been implicated in numerous inflammatory disorders. In many models of acute and chronic inflammatory diseases, blockade of CXCR2 substantially reduces leukocyte recruitment, tissue damage and mortality.

2. Qiu, Y. et al., Thorax. 2007 Mar. 21, reported that in severe exacerbations of asthma there was a bronchial mucosal neutrophilia, eosinophilia and up-regulation of CXC chemoattractants and their receptors. In particular, CXCR2 showed an association with eosinophilia representing a target for treatment in exacerbations of asthma.

3. Rios-Santos, F. et al., Am. J. Respir. Crit. Care Med. 175:490-497 (2007), reported that down-regulation of CXCR2 on neutrophils in severe sepsis was mediated by inducible nitric oxide synthase-derived nitric oxide.

4. Stefanovic, L. et al., J. Interferon Cytokin Res. 26:760-770 (2006), reported that CXCR2 was upregulated in liver in association with profibrotic genes, and

the upregulation could contribute to the poor prognosis in liver patients with elevated levels of CXC chemokines.

5. Cataisson, C. et al., J. Clin. Invest. 116:2757-2766 (2006), reported on the clinical relevance of CXCR2 ligands in intraepidermal inflammation. MIP-2 and KC (a cytokine-induced neutrophil chemoattractant) mediated the infiltration of neutrophils into the epidermis. This infiltration was prevented by ablating CXCR2 in mice transgenic for an inducible intraepidermal inflammation. Thus, CXCR2 is specifically implicated in development of skin inflammation.

6. Busch-Peterson, J., Curr. Top. Med. Chem. 6:1345-1352 (2006), discusses the use of small molecule antagonists of CXCR1 and CXCR2 as effective inhibitors of inflammation in both animal models and human patients. This publication confirms applicant's use of CXCR1 and CXCR2 inhibitors for treating inflammation generally.

7. Donnelly, L.E. et al., Trends Pharmacol. Sci. 27:546-553 (2006), supports the use of CXCR2 inhibitors for reducing inflammation related to chronic obstructive pulmonary disease, for which there is a need in the art, as confirmed by this publication.

8. Boisvert, W. A. et al., Am. J. Pathol. 168:1385-95 (2006), reported that up-regulation of a CXCR2 ligand plays a role in inflammation associated with artherosclerosis. Specifically, CXCR2 expression was important to macrophage accumulation in established artherosclerotic lesions. Thus, antagonists of CXCR2 will play a role in artherosclerosis-related inflammation.

The references cited above are a representative sample of current research that confirms the role of CXCR2 in a wide variety of inflammatory conditions, including skin, lung, liver and septicemia. Small molecules that target the CXCR2 chemokine are already in human clinical trials, as discussed in Exhibit 9. In a Phase I study, in subjects treated with a small molecule CXCR2 antogonist, neutrophilia induction was inhibited. This is important clinically because neutrophils are believed to play a key role in COPD.

Exhibit 9 also confirms the earlier work of other publications suggesting an important role of CXCR2 chemokine in inflammation, and the rationale for inhibiting this chemokine to achieve a reduction in inflammation. The broader applications of such inhibitors to other diseases involving inflammation are discussed in Wislez, M. et al.,

Cancer Res. 66:4198-4207 (2006), Exhibit 10. Kras mice develop lung adenocarcinoma because of somatic activation of an oncogene. CXCR2 ligands contribute to malignancy via neutrophil inflammation. Treatment of Kras mice with a CXCR2-neutralizing antibody inhibited the progression of premalignant alveolar lesions, and induced apoptosis of vascular endothelial cells within alveolar lesions.

Finally, Garau, A. et al., Eur. Cytokine Netw. 17:35-41 (2006), Exhibit 11, describe an inhibitor of CXCR1 and CXCR2 and tested it in a rat model of cerebral ischemia/reperfusion. The molecule decreased polymorphonuclear cell infiltration and infarct size, and significantly improved neurological function. The authors conclude that CXCR1, CXCR2, and their ligands have a role in the inflammatory component of cerebral ischemia. They also conclude that these pathways represent an important pharmacological target.

Applicants have provided new small molecules for this precise target. The publications cited herein amply demonstrate how targeting one pathway can resolve or inhibit inflammation in a broad range of diseases and conditions.

Applicants disagree with the Examiner's assertion that use of a compound or genus against inflammation generally is contrary to medical science. One has only to look at aspirin, and its labeled use for relieving, among other conditions, headaches, muscle pain, toothache, pain and fever of colds, and minor pain of arthritis, as indicated on a Bayer® aspirin label. This covers "virtually any part of the body" as indicated by the Examiner, at page 7, line 1 of the Office Action.

At pages 7-15 of the Office Action, the Examiner lists a range of inflammatory events. Many of these are addressed by the references cited herein as Exhibits 1-11. Applicants have disclosed new inhibitors of a pathway that, as evidenced by the cited references, is a common denominator in a wide range of inflammatory conditions: CXCR1 and CXCR2 pathway. The existence of other treatments for some of the conditions listed by the Examiner does not negate the usefulness of a new range of compounds against the underlying mechanisms of inflammation, despite the Examiner's citation of Cummings, J. et al. at page 3, lines 7-10, of the Office Action.

In view of the foregoing remarks, applicants submit that the Examiner has not met her burden of making a *prima facie* showing that undue experimentation is required

in order to practice the invention as claimed. Reconsideration and withdrawal of this rejection are respectfully requested.

Claims 31-42 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. The Examiner states that if the R5 is an H and linked via a C1 alkylene, it is unclear how it would have a hetero atom also. Applicants have amended claim 31 to remedy the claim language, and request reconsideration and withdrawal of the rejection.

Commissioner is hereby authorized to charge the required fees to Deposit Account No. 04-0258. If additional fees are believed necessary, the Commissioner is further authorized to charge any deficiency or credit any overpayment to Deposit Account No. 04-0258.

All of the claims remaining in the application are now believed to be allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

If questions remain regarding this application, the Examiner is invited to contact the undersigned at (206) 757-8122.

Respectfully submitted,
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